

(19)



Europäisches Patentamt

European Patent Office

Office européen des brevets



(11)

**EP 1 210 946 A1**

(12)

**EUROPEAN PATENT APPLICATION**

(43) Date of publication:

**05.06.2002 Bulletin 2002/23**

(51) Int Cl.<sup>7</sup>: **A61K 35/78**, A61K 31/60,

A61K 47/10, A61P 17/00,

A61P 17/12

(21) Application number: **01310083.9**

(22) Date of filing: **30.11.2001**

(84) Designated Contracting States:

**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU  
MC NL PT SE TR**

Designated Extension States:

**AL LT LV MK RO SI**

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(30) Priority: **01.12.2000 US 728012**

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(54) **Astringent composition and method of use**

(57) The invention provides for astringent compositions comprising from about 0.1% to about 20% by weight of an astringent and between about 0.1% to 10% by weight of alcohol. The compositions have viscosity values of at least about 5,000 centipoise. The invention

also provides for a method of using such compositions for delivering a topically active agent, such as, salicylic acid, into skin.

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## Description

### Field of the Invention

5 [0001] The present invention relates to astringent compositions. The invention also relates to a method of using the compositions for delivering topically active agents into skin.

### Background of the Invention

10 [0002] Astringents are known in the art for use in tightening or binding soft tissue, and toning and moisturizing skin. Commercially available astringent compositions typically comprise very high amounts of alcohol, for example 35-45% by weight, and are liquids having a low viscosity. These compositions can be excessively drying and irritating to skin due to their high alcohol content. Additionally, the nature of their consistency and alcohol levels can make it difficult to control when applying. For example, if a consumer chooses to use only their hands for applying the astringent, then a  
15 greater volume and a larger application is needed for a targeted skin area due to the ease of astringent flow both during the transition from the container to one's hands and from one's hands to the targeted skin area. On the other hand, if a bath implement is used for applying the astringent, for example a cloth or cotton ball, then the thin consistency of the astringent results in some of the astringent being rapidly absorbed by the implement. Any absorbed astringent is then unavailable for use. Small quantities of astringent can also be lost through volatilization from its high alcohol levels.

20 [0003] The present invention provides for viscous and low alcohol content astringent compositions that can be used for delivering topically active agents into the skin.

### Summary for the Invention

25 [0004] According to one aspect of the present invention there has now been provided an astringent composition including about 0.1 % to about 20% by weight of an astringent and between about 0.1 % to 10% by weight of an alcohol; wherein the composition has a viscosity of at least about 5,000 centipoise. In one embodiment, the composition further comprises a topically active agent, such as a karatolytic agent (e.g., salicylic acid) into skin. The present invention also features methods of using the above compositions.

30 [0005] Additional features and advantages of the present invention will be apparent from the detailed description of the invention and from the claims.

### Detailed Description of the Invention

35 [0006] It is believed that one skilled in the art can, based upon the description herein, utilize the present invention to its fullest extent. The following specific embodiments are to be construed as merely illustrative and not limitative of the remainder of the disclosure in any way whatsoever.

[0007] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention belongs. Also, all publications, patent applications, 40 patents, and other references mentioned herein are incorporated by reference.

[0008] The present invention relates to astringent compositions having relatively low levels of alcohol and high viscosity values that, in one embodiment, can be used to deliver topically active agents into skin. In one embodiment, the composition comprises an astringent and an alcohol, wherein the composition has a viscosity of at least about 5,000 centipoise. While wishing not to be bound by a particular theory, it is believed that the high viscosity nature of the  
45 compositions provide occlusivity to skin, thereby holding the composition on the skin, while the alcohol delivers the topically active agent into the skin. The viscosity of the composition also assists in minimizing any loss of alcohol to the environment surrounding the application site, thereby enhancing the delivery of the active agent. As shown below in Example 3, it was also discovered that lower amounts of alcohol results in a greater percentage of active delivered from the composition into the skin as compared to compositions having higher amounts of alcohol.

50 [0009] Astringents are generally included in the compositions to help promote the binding and tightening of soft tissue and to tone skin. Any astringents known to one having ordinary skill in the art can be used in the present invention. Natural as well as synthetic astringents may be used. A representative, non-limiting list of natural astringents, include aluminum citrate, aluminum lactate, extracts of birch, extracts of coffee, extracts of evening primrose, extracts of grape, extracts of henna, extracts of ivy, extracts of lemon, and extracts of witch hazel. What is meant by an extract is either  
55 the whole fruit, bean, and/or plant or select constituents of such fruit, bean, and/or plant. The amount of astringent in the present invention is from about 0.1% to about 20% by weight, based on the total weight of the composition. In one embodiment, the astringent comprises an extract of witch hazel in an amount of about 10% by weight of the composition.

[0010] What is meant by the term "alcohol" is ethanol or isopropyl alcohol. Typically astringent compositions contain

alcohol at levels of around 35-45% by weight. Compositions of the present invention comprise alcohol between about 0.1% to 10% by weight, preferably, less than about 5% by weight of the composition. Surprisingly, such low levels of alcohol were found to more effectively deliver active agents into the skin. As is shown in Example 3, astringent compositions containing about 5% ethanol delivered a greater percentage of an active agent into the skin than astringent compositions containing about 10% ethanol.

**[0011]** Compositions of the present invention have viscosity values of at least about 5,000 centipoise, preferably of at least about 10,000 centipoise. One embodiment of the present invention has a viscosity of about 12,500 centipoise. One means of obtaining the recited viscosity values is by adding a viscosity-increasing agent to the compositions, for example, a polyvinyl methacrylate/methyl acrylate crosspolymer. Other viscosity-increasing agents include, but are not limited to, bentonite, carbomer, carrageenan, ozokerite, dextrin, gelatin and cellulose resin such as xanthan gum. Additional viscosity-increasing agents are found in the International Cosmetic Ingredient Dictionary and Handbook, eds. Wenninger and McEwen, pp. 1693-1697 (The Cosmetic, Toiletry, and Fragrance Assoc., Washington, D.C., 7<sup>th</sup> Ed., 1997) (hereinafter "ICI Handbook"). In one embodiment, the viscosity-increasing agent is present in an amount from about 0.02% to about 5% by weight of the composition.

**[0012]** Compositions of the present invention may further include topically active agents. What is meant by a "topically active agent" is a compound that has a cosmetic, prophylactic or therapeutic effect on the skin, e.g., agents to block UV rays, treat wrinkles and/or acne, or to lighten the skin. In one embodiment, the agent is selected from, but not limited to, the group consisting of hydroxy acids, benzoyl peroxide, sulfur resorcinol, ascorbic acid, D-panthenol, hydroquinone, sunscreen agents, keratolytic agents, antiinflammatory agents, skin lightening agents, antimicrobial and antifungal agents, estrogens, 2-dimethylaminoethanol, lipoic acid, amino acids such as proline and tyrosine, lactobionic acid, acetyl-coenzyme A, niacin, riboflavin, thiamin, ribose, electron transporters such as NADH and FADH<sub>2</sub>, botanical extracts such as aloe vera and soy, and derivatives and mixtures thereof. The topically active agent will typically be present in the composition of the invention in an amount between about 0.01% to about 20% by weight of the composition.

**[0013]** Examples of hydroxy acids include, but are not limited, to (i) alpha-hydroxy acids such as glycolic acid, lactic acid, malic acid, citric acid, and tartaric acid, (ii) beta-hydroxy acids such as salicylic acid, and/or (iii) polyhydroxy acids. See, e.g., European Patent Application No. 273,202.

**[0014]** Examples of derivatives of ascorbic acid include, but are not limited to, ascorbyl palmitate, magnesium ascorbyl phosphate, sodium ascorbyl phosphate, zinc ascorbyl phosphate, ascorbyl glucoside, sodium ascorbate, and ascorbyl polypeptide. An example of a derivative of hydroquinone includes, but is not limited to, arbutin.

**[0015]** In a preferred embodiment, the topically active agent is a keratolytic agent. Exemplary keratolytic agents are salicylic acid, boric acid and methyl salicylate. Compositions of the present invention comprise a keratolytic agent in an amount from about 0.1% to about 5% by weight, preferably from about 0.5% to about 2% by weight of the composition. In one embodiment salicylic acid is present in an amount of about 2% by weight of the composition.

**[0016]** Solubilizers for the optional topically active agent may also be employed. Preferably, such solubilizers are oil-free, compatible with alcohol, and do not crystallize the topically active agent. Examples of solubilizers include, but are not limited to, polyethylene glycol, polyethylene glycol ethers of fatty alcohols, and mixtures thereof. Solubilizers are present in amounts sufficient to solubilize such topically active agent(s).

**[0017]** In one embodiment, the compositions further comprises a skin-soothing agent. Exemplary skin-soothing agents are extracts from Aloe Vera and Chamomile and mixtures thereof. Skin-soothing agents are typically present in amounts from about 0.1% to about 5% by weight of the composition.

**[0018]** In preferred embodiments, the composition comprises less than 1%, by weight, of oil or does not comprise any oil. What is meant by the term "oil" is an animal (e.g., fatty acid esters), mineral (e.g., paraffinic oils), vegetable (e.g., vegetable oils), or synthetic hydrocarbons that are liquid at room temperature, soluble in organic solvents, and substantially not soluble in water (e.g., less than 0.1 mg/ml at 25°). Examples of oils include but are not limited to: mineral oils such as paraffinic oils; synthetic hydrocarbons such as polybutene and polyisobutene; vegetable oils such as castor oils, sesame oils, and peanut oils; and animal oils and fats such as triglycerides and butters. Other examples of fats, oils, and hydrocarbons are found in the International Cosmetic Ingredient Dictionary and Handbook, eds. Wenninger and McEwen, pp. 1565-67 and 1574-75 of the ICI Handbook.

**[0019]** The novel compositions of the present invention may also contain other cosmetic ingredients such as humectants, emollients, skin-conditioning agents, skin protectants, colorants, fragrances and the like. Examples of such may be found on pages 1628-1630, 1639-1640, 1650-1651, 1656-1670 of the ICI Handbook.

**[0020]** The compositions of the present invention may be applied to the skin (e.g., the face of a human). In one embodiment, the composition may be applied once or twice a day. In one embodiment, the composition is applied to the skin by first applying to the hands and then rubbing it onto the target skin area. In another embodiment, the composition is applied to a bath implement, such as a cotton ball or a cloth, and then applied to the target skin area.

**[0021]** The following is a description of the manufacture and testing of astringent compositions. Other compositions of the present invention can be prepared in an analogous manner by a person of ordinary skill in the art.

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### Example 1

**[0022]** A substantially oil-free astringent composition (formulation A) was made with the following ingredients and corresponding amounts.

Ingredient	Weight Percentage
Purified water	q.s. 100
Polyvinyl methacrylate/methyl acrylate crosspolymer	1.8
Allantoin	0.08
Chloeth-24 & Ceteth-24 (50:50)	0.2
Salicylic acid	2
Glycereth-7	2
Polyethylene glycol-4	1
Dimethicone copolyol	1
Hexylene glycol	2
Witch hazel	10
Benzophenone-4	0.03
Sodium hydroxide (50%)	1.5
Sodium PCA	1
Menthol	0.05
Extract of Aloe Vera	0.2
Extract of Chamomile	0.2
Ethanol mixture (95 % ethanol)	5
Colorant	q.s.
Fragrance	q.s.

**[0023]** Formulation A was made by the following procedure. Approximately 80-90% of the quantity of purified water was heated to 75°C, and the allantoin and polyvinyl methacrylatemethyl acrylate crosspolymer were added thereafter. These ingredients were mixed for approximately 30 minutes. Chloeth-24 and Ceteh-24 were then added, and the batch mixed until all of the solids were dissolved. Following this, the batch was cooled to about 50-55°C. Next, the salicylic acid, glycereth-7, PEG-4, and dimethicone copolyol were added, with continuous mixing sufficient to completely dissolve the salicylic acid. Hexylene glycol was then added, thereby dropping the batch temperature, whereupon witch hazel (Manamelis Virginiana (containing 14% ethanol); The EE Dickinson Company, Essex, Connecticut, USA) was added when the temperature reached about 40-45°C. Benzophenone-4, sodium hydroxide, and the remaining portion of purified water were added with 3 minutes of mixing between each addition. The batch was mixed until a homogenous blend was achieved. With the batch at 40°C, sodium PCA, menthol, and the natural extracts of Aloe Vera and Chamomile were added, with 3 minutes of mixing between each addition. The batch was then allowed to cool to 35°C, whereupon the ethanol mixture (SD-40 Alcohol; Quantum Chemical, Cincinnati, Ohio, USA) was added. Lastly, the colorant and fragrance were added with 5 minutes of mixing between each addition.

### Example 2

**[0024]** A second astringent composition (formulation B) was made with the difference from example 1 above being the addition of about 10% by weight of the ethanol mixture as compared to about 5% by weight of the ethanol mixture.

### Example 3

**[0025]** Penetration studies were conducted on eight panelists to determine the amount of salicylic acid that had penetrated into their skin. The amount of salicylic acid was determined using a Perkin Elmer Spectrofluorometer (Nor-

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walk, Connecticut, USA) equipped with a fiber optic probe. Specific areas on the subjects' skin were monitored at time zero, 3 hours, and 6 hours after the initial application, and subsequently wiping off the product from the applied areas. Surprisingly, a greater percentage of salicylic acid penetrated the skin with the product having the lower amount of alcohol as shown in the table below.

Product	% Penetration v. Form. A, after 3 hours	% Penetration v. Form. A, after 6 hours
Formulation A (5% alcohol)	100	100
Formulation B (10% alcohol)	86	93

### Example 4

[0026] Compositions of the present invention have viscosity values of at least about 5,000 centipoise. Viscosity measurements taken from formulation A are shown in the table below. A Brookfield RVT Spindle TB viscometer (Stoughton, Massachusetts, USA) was used for evaluating the viscosity of the samples. The samples were surrounded by a water bath environment at a temperature of 25°C. A Helipath drive motor was used to rotate a T-bar spindle just above the surface of each sample. The Helipath drive was started in the downward direction, with a reading taken every rotation. After 6 readings were recorded, the direction of the Helipath drive was reversed, and 6 additional readings were taken, one per rotation of the spindle. The values shown in the table below are averages from the 12 readings. The compositions are somewhat thixotropic in nature, resulting in viscosity creep over time.

Age, time after batch completion	Viscosity, cps
1 hour	11,960
18 hours	11,993
24 hours	12,120
2 days	12,120
3 days	12,133
4 days	12,446
7 days	12,580

[0027] It is understood that while the invention has been described in conjunction with the detailed description thereof, that the foregoing description is intended to illustrate and not limit the scope of the invention, which defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the claims.

### Claims

1. An astringent composition comprising:

- (a) from about 0.1% to about 20% by weight of an astringent; and
- (b) between about 0.1 % to 10% by weight of alcohol;

wherein said composition has a viscosity of at least about 5,000 centipoise.

2. The composition of claim 1, wherein said astringent is selected from the group consisting of aluminum citrate, aluminum lactate, extract of birch, extract of coffee, extract of evening primrose, extract of grape, extract of henna, extract of ivy, extract of lemon, and mixtures thereof.

3. The composition of claim 1, wherein said astringent is an extract of witch hazel.

4. The composition of any preceding claim, wherein said composition comprises from about 0.02% to about 5% by weight of a viscosity-increasing agent.

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5. The composition of claim 4, wherein said viscosity increasing agent is polyvinyl methacrylate/methyl acrylate cross-polymer.
6. The composition of any preceding claim having a viscosity of at least about 10,000 centipoise.
7. The composition of any preceding claim, wherein said alcohol is ethanol.
8. The composition of any preceding claim, wherein the amount of said alcohol is less than about 5% by weight of the composition.
9. The composition of any preceding claim further comprising from about 0.1% to about 5% by weight of a skin soothing agent, wherein said skin soothing agent is selected from the group consisting of extracts of Aloe Vera, extracts of Chamomile, and mixtures thereof.
10. The composition of any preceding claim, wherein said composition comprises less than 1%, by weight, of oil.
11. The composition of any preceding claim, further comprising a topically active agent.
12. The composition of claim 11 wherein the amount of said topically active agent is from about 0.01% to about 5% by weight of the composition.
13. The composition of claim 11, wherein the amount of said topically active agent is from about 0.5% to about 2% by weight of the composition.
14. The composition of any of claims 11 to 13 wherein said topically active agent is a keratolytic agent.
15. The composition of claim 14, wherein the keratolytic agent is salicylic acid.
16. The composition of claim 15 further comprising a solubilizer in an amount to solubilize said salicylic acid.
17. The composition of claim 16, wherein said solubilizer is selected from the group consisting of polyethylene glycol, polyethylene glycol ethers of fatty alcohols, and mixtures thereof.
18. A composition according to any of claims 11 to 17 for use in therapy.



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# EUROPEAN SEARCH REPORT

Application Number  
EP 01 31 0083

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	WO 97 14401 A (KAO CORPORATION) 24 April 1997 (1997-04-24) * examples 8,10,13,14 *	1-13,18	A61K35/78 A61K31/60 A61K47/10 A61P17/00 A61P17/12
X	US 5 073 366 A (BECK FRED) 17 December 1991 (1991-12-17) * abstract *	1-4,7,9,11,18	
X	WO 00 47167 A (COLOR ACCESS INC) 17 August 2000 (2000-08-17) * page 8, line 16 - line 24 * * examples *	1-3,11,18	
X	WO 93 21899 A (PROCTER & GAMBLE) 11 November 1993 (1993-11-11) * page 7 - page 12 * * claims 1-6 *	1-18	
X	EP 0 335 403 A (SANSHO SEIYAKU KK ;HAYASHI TERUAKI (JP)) 4 October 1989 (1989-10-04) * examples *	1,7	
X	DATABASE WPI Derwent Publications Ltd., London, GB; AN 1997-316445 XP002192266 & JP 09 124441 A (ADERANS KK), 13 May 1997 (1997-05-13) * abstract *	1-18	TECHNICAL FIELDS SEARCHED (Int.Cl.7) A61K
X	DATABASE WPI Derwent Publications Ltd., London, GB; AN 1992-180097 XP002192267 & JP 04 117314 A (KANEBO LTD.), 17 April 1992 (1992-04-17) * abstract *	1,7,11,18	
The present search report has been drawn up for all claims			
Place of search <b>MUNICH</b>		Date of completion of the search <b>6 March 2002</b>	Examiner <b>Pacreu Largo, M</b>
<p><b>CATEGORY OF CITED DOCUMENTS</b></p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons &amp; : member of the same patent family, corresponding document</p>			

EPO FORM 1503 03/02 (P04C01)



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Office

# EUROPEAN SEARCH REPORT

Application Number  
EP 01 31 0083

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
A	WO 98 50005 A (MEDLOGIC GLOBAL CORP) 12 November 1998 (1998-11-12) * figure 8 * -----	1-18	
			TECHNICAL FIELDS SEARCHED (Int.Cl.7)
The present search report has been drawn up for all claims			
Place of search MUNICH		Date of completion of the search 6 March 2002	Examiner Pacreu Largo, M
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone  Y : particularly relevant if combined with another document of the same category  A : technological background  O : non-written disclosure  P : intermediate document</p> <p>T : theory or principle underlying the invention  E : earlier patent document, but published on, or after the filing date  D : document cited in the application  L : document cited for other reasons  &amp; : member of the same patent family, corresponding document</p>			

EP 0 FORM 1503 (03.92) (P44C01)

**ANNEX TO THE EUROPEAN SEARCH REPORT  
ON EUROPEAN PATENT APPLICATION NO.**

EP 01 31 0083

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on  
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06-03-2002

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 9714401	A	24-04-1997	JP	9110667 A	28-04-1997
			JP	9165313 A	24-06-1997
			JP	9208442 A	12-08-1997
			CN	1166135 A	26-11-1997
			EP	0805674 A1	12-11-1997
			WO	9714401 A1	24-04-1997
			US	6348200 B1	19-02-2002
-----					
US 5073366	A	17-12-1991	NONE		
-----					
WO 0047167	A	17-08-2000	AU	2416400 A	29-08-2000
			WO	0047167 A1	17-08-2000
-----					
WO 9321899	A	11-11-1993	CA	2134979 A1	11-11-1993
			EP	0639068 A1	22-02-1995
			JP	7506367 T	13-07-1995
			WO	9321899 A1	11-11-1993
			US	5612324 A	18-03-1997
			US	5710141 A	20-01-1998
-----					
EP 0335403	A	04-10-1989	JP	1249713 A	05-10-1989
			DE	68903241 D1	26-11-1992
			DE	68903241 T2	27-05-1993
			EP	0335403 A2	04-10-1989
			US	4981485 A	01-01-1991
-----					
JP 9124441	A	13-05-1997	NONE		
-----					
JP 4117314	A	17-04-1992	NONE		
-----					
WO 9850005	A	12-11-1998	AU	7472398 A	27-11-1998
			EP	1011609 A1	28-06-2000
			WO	9850005 A1	12-11-1998
-----					